REMARKS

Claims 27, 46 and 48 are amended. Following entry of this amendment, claims 27-32, 34-38, 43-44, 46, 48, and 51-53 will be pending in this application.

Applicants have amended claims 27, 46 and 48 to specify that the methods are for reducing spatial or declarative memory dysfunction caused by damaged hippocampal tissue. Support for this amendment may be found, for example, at specification page 48, lines 10-18 and page 49, lines 3-16.

None of the amendments introduces any new matter.

THE REJECTIONS

35 U.S.C. §112, First Paragraph - Enablement

Claims 27-38, 43-44, 46, 48 and 51-53

The Examiner has rejected claims 27-38, 43-44, 46, 48 and 51-53 under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that the specification, while enabled for "up-regulating the expression of N-CAM and L1 in NG108-15 cells and increasing dendritic arbors of 7-14 DIV cultured hippocampal neurons with OP-1", does not provide enablement for a method for reducing memory dysfunction associated with damaged hippocampal tissues and caused by permanent or global ischemia comprising determining the existence of memory dysfunction and administering a structurally ill-defined morphogen merely comprising a conserved C-terminal seven-cysteine skeleton that is at least about 60% identitical or 70% homologous to residues 330-

431 of human OP-1 or fragments thereof. The Examiner contends that the instant claims encompass uncharacterized and undefined memory dysfunction and memory dysfunction or deficit is a complex process and its cause or process is not clear. The Examiner states that it is unpredictable whether the claimed method can truly reduce memory dysfunction. The Examiner further contends that neither the specification nor the prior art show that the claimed morphogens with limited homology are effective in treatment of reduced undefined or uncharacterized memory dysfunction, it is unpredictable whether these claimed morphogens would truly work in the claimed method.

Applicants traverse. However, solely to expedite prosecution of this application, applicants have amended claims 27, 46 and 48 (and therefore, claims dependent therefrom) to recite a method for reducing spatial or declarative memory dysfunction caused by damaged hippocampal tissue. Applicants respectfully submit that the claims, as amended, are fully enabled by applicants' specification. The specification describes that "memory deficit following direct hippocampal injury or injury to an immediate hippocampal pathway results in a pattern of memory impairment that parallels or mimics the memory dysfunction or amnesia observed in humans following medial temporal damage" (*see*, page 49, lines 3-16). The specification also describes that "cell loss in the hippocampus affects both 'spatial memory' or 'spatial learning',... and general memory function, also referred to as 'declarative memory'" (*see*, page 48, lines 10-18). In addition, as shown in the "Bioassay" section (*see*, page 55, line 9 to page 61, line 7), upon administration of morphogens, cells exhibit changes in biochemical

characteristics (N-CAM expression) and dendrite growth. Dendrite density correlates with retention of memory function in normal aging brain (Morrison et al., of record). Further, it has been previously shown that morphogens indeed enhance synaptic regeneration in vitro (See US Pat. No. 6,506,729, especially Example 16) and, in fact, nerve gap repair was seen. (ibid., Example 9). One of skill in the art would readily recognize, based on these observations, that the morphogens of the present application would enhance synaptic regeneration of damaged hippocampal tissue which would lead to increased dendrite density and reduced spatial or declarative memory dysfunction. Accordingly, applicants' specification provides sufficient disclosure to support the claimed method for reducing spatial or declarative memory dysfunction caused by damaged hippocampal tissue.

With respect to the Examiner's contentions that applicants' specification does not provide sufficient disclosure to demonstrate that the claimed method is enabled for any amino acid sequence having 60% identity or 70% homology to OP-1, applicants traverse. As described in the specification and reflected in the amended claims, the distinguishing structural feature that is conserved among all species of the claimed genus is the seven-cysteine skeleton, which is defined by residues 330-431 of SEQ ID NO:2. The conserved 330-431 residues that are specified in SEQ ID NO: 2 have been retained throughout various morphogens of different species in this superfamily, indicating the structural or chemical significance that caused these residues to be evolutionarily preserved. The study of crystal structures of OP-1 and TGF-beta revealed a surprising similarity in the structure despite the low

overall amino acid identity, indicating that the protein tolerates diverse substitutions to retain its three-dimensional structure. *See*, for example, Griffith, et al., Proc. Natl. Acad. Sci. USA, 93:878-883 (1996) ("Griffith", submitted herewith as Exhibit A). It has been shown that OP-1, an exemplary morphogen, loses its activities when reduced (*see*, for example, US Pat. No. 5,011,691 (the "'691 patent"), at column 7, lines 20-24, incorporated by reference on page 18, lines 15-16), indicating the importance of the conserved cysteine residues that are able to form disulfide bonds and are responsible for producing an active protein.

Using the positional locations of cysteine residues conserved among the morphogens, the specification also describes the generation of biosynthetic constructs which may be useful morphogens of the invention. For example, on page 18, lines 15-16, the specification incorporates by reference the disclosure of the '691 patent, which relates to the creation of biosynthetic constructs (COP-1, COP-3, COP-4, COP-5, COP-7 and COP-16) from the consensus amino acids encompassing several naturally occurring morphogens. The sequences of the seven-cysteine domain of COP-5 and COP-7 both share approximately 78% homology with the OP-1 seven-cysteine domain sequence, indicating these polypeptides fall within the scope of the claimed invention. The '691 patent also demonstrated that both COP-5 and COP-7 proteins enhanced bone and cartilage formation *in vivo* in a manner analogous to naturally occurring OP-1. Because they demonstrate similar physiological activity to OP-1, COP-5 and COP-7 are also expected to behave similarly to OP-1 in other aspects of their morphogenic activity. Applicants submit that the incorporation by reference of COP

protein data gives further support to the scope of the claims. Accordingly, applicants' specification provides more than adequate disclosure to support any amino acid sequence having 60% identity or 70% homology to residues 330-431 of SEQ ID NO:2.

In view of the claim amendments and arguments presented above, applicants respectfully request that the Examiner withdraw this rejection.

Claim rejection under 35 USC 103(a)

The Examiner has rejected claims 27-32, 34-38, 43, 44, 46, 48, and 51-53 under 35 U.S.C. 103(a) as being obvious over the teaching of U.S. Patent 6,723,698 ("Rueger") in view of Bachevalier et al., "Cerebral Ischemia: Are the Memory Deficits Associated with Hippocampal Cell Loss?", Hippocampus, 6:553-560 (1996)("Bachevalier"), Contestabile et al. "Effects of Short and Long-Term Ganglioside Treatment on the Recovery of Neurochemical Markers in the Ibotonic Acid-Lesioned Rat Striatum," J. Neurosci. Res., 26:483-7 (1990)("Contestabile"), Simonsen et al. "Methodological approaches to the evaluation of neurotoxicity data and the classification of neurotoxic chemicals," Scand. J. Work Environ. Health., 20:1-12 (1994)("Simonsen") and Gillette-Guyonnet et al. "Weight loss in Alzheimer disease," Am. J. Clin. Nutr., 71:637S-642S (2000)("Gillette-Guyonnet") and an evidentiary reference Holownia et al. "Accumulation of ammonia and changes in the activity of some ammonia metabolizing enzymes during brain ischemia/reperfusion injury in rats," Mater Med. Pol. Jan-Mar; 26:25-7 (1994)("Holownia").

Applicants assert that Rueger does not qualify as prior

art. Applicants submit that Rueger was subject to assignment to Creative Biomolecules, Inc. at the time of the invention disclosed therein. The present application was also subject to assignment to Creative Biomolecules, Inc. at the time of the invention disclosed within the present application. Under 37 C.F.R. 1.104(c)(4), "[s]ubject matter which is developed by another person which qualifies as prior art only under 35 U.S.C. 102(e), (f) or (g) may be used as prior art under 35 U.S.C. 103 against a claimed invention unless the entire rights to the subject matter and the claimed invention were commonly owned by the same person or organization or subject to an obligation of assignment to the same person or organization at the time the claimed invention was made," (emphasis added).

Rueger qualifies as 102(e) prior art because it has an earlier priority date than the present application but was not published under 35 U.S.C. 122(b) before the present invention. Therefore, the Rueger would qualify as prior art only under 35 U.S.C. 102(e) for 103 purposes. Submitted herewith are Assignments showing that all rights in Rueger and all rights in the instant application (via assignment of the parent application 09/012,846) were assigned to Creative Biomolecules, Inc. at the time the claimed invention was made (Exhibit B). In view of the two Assignments, it is asserted that Rueger does not qualify as prior art.

None of the other cited references remedy the deficiencies. Accordingly, applicant respectfully requests this rejection be withdrawn.

35 U.S.C. §112, First Paragraph - Written description

Claims 34-35

The Examiner has rejected claims 34-35 under 35 U.S.C. §112, first paragraph, for lack of written description. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time of filing. Specifically, the Examiner asserts that the specification fails to disclose the limitation of "a morphogen comprising residues 293-431 of SEQ ID NO:2."

Applicants traverse. Claims 34 and 35 recite the amino acid residues that comprise the mature OP-1 peptide. Description of the mature OP-1 peptide is found on page 8, lines 6-9 and page 12, lines 11-12 of the specification. The recitation of the mature OP-1 peptide comprising residues 293-431 of SEQ ID NO:2 is supported by US Pat. No. 5,266,683, which is incorporated by reference in the instant application (*see*, page 17, lines 22-23). The Examiner contends that, because multiple forms of OP-1 are disclosed in the '683 patent, the support is not adequate. However, upon careful reading of the '683 patent, only the form having amino acid residues 293-431 of human OP-1 is referred to as "mature OP-1" (see column 16, lines 6-9); other forms are referred to as a "short form of OP-1" and "N-terminally truncated mature OP-1". They may all be morphogenetically active, but are clearly differentiated from the mature form of OP-1. The mature OP-1 protein is also described in the '683 patent as having 139 amino acid residues (see column 7, lines 9-10). Thus, applicant submits that there is a clear and unambiguous support in the '683 patent for the recitation of "mature OP-1."

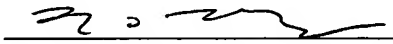
Accordingly, the specification provides more than adequate written description to support the claimed fragments of SEQ ID NO:2 and applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants request that the Examiner reconsider and withdraw all outstanding rejections and allow the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled by telephone to expedite allowance of the pending claims.

Respectfully submitted,



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